REMARKS

Upon entry of this amendment, claims 1-32 are pending. Among them, claims 1-12, 16-19, and 22-26 are currently under consideration. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Election/Restriction

Claims 27-32 are withdrawn from consideration as being directed to a non-elected invention. Applicants will cancel these claims, if necessary, upon indication of allowable subject matter.

Claims 13-15 and 20-21 are withdrawn from consideration as being directed to non-elected species. Applicants respectfully point out that claim 9, upon which claims 13-15 depend, is a generic claim linking elected and non-elected species; claim 19, upon which claims 20 and 21 depend, is a generic claim linking elected and non-elected species. Applicants reiterate that Applicants are entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claims as provided by 37 CFR 1.141 (MPEP 809.02(a)). Furthermore, the burden is on the Examiner to examine these generic claims throughout their scope, together with any claims dependent thereon drawn to non-elected species or inventions, rather than for Applicants to limit the scope of the generic claims to conform to the scope of any species or inventions listed in a Restriction Requirement.

Specification Objections

The Office Action objects to the specification because the application does not contain an abstract. Applicants submit that an abstract is present in the PCT phase of the instant application

(see first page of the published PCT application WO 99/21574). Nevertheless, Applicants have amended the specification to include an Abstract page as the last page of the specification. Reconsideration and withdrawal of the objection is respectfully requested.

The Office Action also objects to the specification for not containing, either in the first sentence of the specification or in an application data sheet, a priority claim. Applicants have amended the specification to insert the proper priority claim. Reconsideration and withdrawal of the objection is respectfully requested.

The Office Action also requires Applicants to update the status of patent applications through out the specification. Applicants have amended the specification to obviate this objection. Reconsideration and withdrawal of the objection is respectfully requested.

Claim Objections

Claims 8-9, 11, 16-17, 19, and 26 are objected to because claims 8-9, 16-17, 19, and 26 recite non-elected species, and that "CTNF" in claim 11 is apparently a typographical error.

Applicants have amended claim 11 to correct the typographical error. There is no narrowing of scope due to this amendment.

However, Applicants submit that claims 8-9, 11, 16-17, 19 and 26 are generic claims linking elected and non-elected species. Pursuant to MPEP 809.02(a), Applicants are entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claims as provided by 37 CFR 1.141 (MPEP 809.02(a)). Furthermore, the burden is on the Examiner to examine these generic claims throughout their scope, together with any claims dependent thereon drawn to non-elected species or inventions, rather than for Applicants to limit the scope of the generic claims to conform to the scope of any species or inventions listed in a Restriction Requirement. Thus, Applicants respectfully request the examination of the full scope of these claims according to the Markush group examination guideline set forth in MPEP 803.02.

Claim rejections under 35 U.S.C. 112, first paragraph

Claims 1-12, 16-19, and 22-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the claimed invention commensurate in scope with these claims.

Specifically, the Office Action asserts that the specification does not teach any methods or working examples that administer any molecule to a mammal and overcome morphogen inhibition to potentiate morphogen activity, promote neuronal cell growth, treat a disorder characterized by neuronal cell loss, or treat a neurodegenerative disorder. The Office Action also asserts that the specification does not disclose administering any molecules to a mammal that are cAMP-dependent messenger pathway inhibitors. Thus, the Office Action concludes that undue experimentation would be needed for a skilled artisan to determine the route, quantity, and duration of administering all possible molecules. The Office Action also contends that pages 2 and 22-24 of the specification regarding morphogen administration is not sufficient guidance, but merely an invitation for further experiments.

Applicants submit that the claimed methods are related since a method for potentiating morphogen activity would, based on the teachings of the instant application and common knowledge in the art at the time of filing, also promote neuronal cell growth, which by definition would be useful for treating disorder characterized by neuronal cell loss, itself a hallmark of neurodegenerative disorders.

Applicants also submit that the specification has clearly provided ample *in vitro* examples of releasing morphogen inhibition, as well as examples of cAMP-dependent messenger pathway inhibitors that can be used for releasing morphogen inhibition. Thus, the rejection relates to *in vitro* and *in vivo* correlation. Pursuant to MPEP 2164.02:

> The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention.

> If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).
>
> Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985).

Evidently, either an *in vitro* or *in vivo* model is sufficient to support the claimed methods, as long as there is correlation between the model and the claimed use. Requiring Applicants to provide an *in vivo* model, even in the presence of a correlating *in vitro* model, is inconsistent with the MPEP guideline set forth above. Applicants submit that using cultured neurons *in vitro* is a proper model that correlates with *in vivo* administering of morphogens. If a molecule (such as anti-LIF Ab) is known to release morphogen inhibition *in vitro*, and leads to dendritic outgrowth as shown in Figure 5, a skilled artisan would reasonably expect that the same molecule would have the same effect on dendritic outgrowth *in vivo*. In contrast, other than simply dismissing the *in vitro* experiments as not correlating with the *in vivo* use, the Office Action provides neither scientific reasoning nor cited references to buttress its argument, thus failing to meet the initial burden required by MPEP to support its argument of non-enablement.

Applicants respectfully remind the Examiner that the Federal Circuit recently articulated a standard whereby the PTO must establish a rational connection between the agency's fact-findings and its ultimate action. *Dickinson v. Zurko*, 119 S.Ct. 1816 (1999). In light of Applicants' arguments of record, the substantial documentation that has been provided, and the presumption in favor of Applicants, it is respectfully asserted that the present rejection is not supported by substantial evidence, and as such, fails to rise above the "arbitrary, capricious" standard applied under the "substantial evidence" test of Section 706(2)(E) of the Administrative Procedure Act. As Applicants point out above, other than stating that there is no *in vivo* and *in*

vitro correlation, the Examiner has not cited any relevant art nor relied on any other fact-finding results to rebut the presumption in favor of Applicants. If the Examiner is relying on personal knowledge, Applicants respectfully request that the Examiner provide an affidavit pursuant to 37 C.F.R. 1.104(d)(2).

In support of Applicants' position that the *in vitro* model is an art-recognized model of studying neuronal growth *in vivo*, Applicants hereby submit two articles in the same field as **Exhibits A** (Guo et al., *Neurosci. Letters* **245**: 131-134) and **B** (Le Roux et al., *Experimental Neurology* **160**: 151-163). In both Exhibits, neurons are cultured *in vitro* using similar conditions, and the effects of morphogens on these neurons are studied so that *in vivo* implications can be ascertained based on these studies. In particular, the last paragraph of **Exhibit B** spanning pages 160-161 discusses the *in vitro* and *in vivo* correlation of these results based on other relevant findings in the field.

Furthermore, Applicants hereby submit **Exhibit C** (WO 97/34626), which demonstrates in the Example section that morphogens can be administered intracisternally to experimental animals (see page 35 and 36). Page 22, line 20, of the instant application refers to intracisternal administration as one of many possible routes of administering morphogens.

Regarding the quantity and duration of treatment, the Office Action also asserts that the claimed method may not necessarily overcome morphogen inhibition to potentiate morphogen activity, etc., since a skilled artisan must resort to trial and error and undue experimentation to determined the optimal dosage, duration and mode of administration of all possible molecules. Applicants submit that page 20, 2nd full paragraph teaches that "[a] method for identifying and testing inducers (stimulating agents) competent to modulate the levels of endogenous morphogens in a given tissue is described in detail in published applications W093/05172 and W093/05751, the teachings of which are incorporated herein by reference. Briefly, candidate compounds can be identified and tested by incubation *in vitro* with a test tissue or cells thereof, or a cultured cell line derived therefrom, for a time sufficient to allow the compound to affect the production, i.e., the expression and/or secretion, of a morphogen produced by the cells of that tissue. Suitable tissue, or cultured cells of a suitable tissue, preferably can be selected from renal epithelium, ovarian tissue, fibroblasts, and osteoblasts."

Based on this teaching, a skilled artisan could readily identify a potential molecule that overcomes morphogen inhibition, and the dose and duration for achieving the effect *in vitro*. These *in vitro* results will in turn guide a skilled artisan to determine a proper dose and duration for *in vivo* use, using merely routine experimentation. Such routine experimentation would require nothing more than trying a range of doses for a range of durations. These variables are routinely varied even for well established medications, since each patient has a unique combination of physiological characteristics. A myriad of elements, such as the height, weight, age, health condition (such as kidney function), prior existing conditions (such as allergy and other medications), gender, and other relevant medical history of the patient are all factors for consideration when determining effective dose and treatment duration. Such considerations are routine in the art. A skilled artisan, such as an attending physician, would readily be able to determine the optimal dosage and duration for individual patients. On the other hand, it would neither necessary nor possible for Applicants for foresee all possible dosages or treatment durations for all molecules, when such information can be routinely obtained.

Claim 17 is rejected as containing subject matter not described in the specification. Specifically, the Office Action points to the typographical mistakes such as "BNT2A," "BW6," etc. as new matter and suggested correction.

Applicants submit that the originally filed claims correctly recite the appropriate names of all morphogens, and such typographical mistake was only inadvertently presented in replying to the first Restriction Requirement dated December 18, 2001. However, Applicants never amended the original claims to introduce such typographical errors, and thus technically these mistakes should not even be in the pending claims. Please also refer to the reply to the second Restriction Requirement, which correctly spells all appropriate morphogen names.

In summary, all amended claims meet the enablement requirement of 35 U.S.C. 112, first paragraph. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim rejections under 35 U.S.C. 112, second paragraph

Claims 1-12, 16-19, and 22-26 are rejected under 35 U.S.C. 112, second paragraph as being indefinite. Particularly, the Office Action asserts that these claims lack a step that clearly relates back to the preamble.

Applicants have amended claims 1 and 4 to obviate this rejection. Applicants submit that the single step of the method comprises administering a molecule that overcomes morphogen inhibition, thus by definition, potentiates morphogen activity, and any other morphogen activity-associated biological effects, as recited in claims 2-4 and their dependent claims.

The Office Action asserts that there is no step indicating how administration of a molecule potentiates morphogen activity. Applicants submit that the molecule administered is not just about any molecule, but rather a molecule "that overcomes morphogen inhibition." Thus, said molecule by definition would release inhibitory effects on morphogen activity, and potentiate any morphogen-stimulated activity.

The Office Action asserts that the term "morphogen activity" is a relative one not defined by claims, and that the specification does not provide a standard for ascertaining the requisite degree, and a skilled artisan would not be reasonably apprised of the scope of the claimed invention. The Office Action seems to hint that a specific activity, such as migration, proliferation etc. would be used for morphogen activity.

Pursuant to MPEP 2173, "[t]he primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent. A secondary purpose is to provide a clear measure of what applicants regard as the invention so that it can be determined whether the claimed invention meets all the criteria for patentability and whether the specification meets the criteria of 35 U.S.C. 112, first paragraph with respect to the claimed invention."

Applicants submit that the instant claimed invention is partly based on the general discovery that morphogen-stimulated activity may be suppressed due to the presence of certain inhibitors of morphogen activity. These inhibitors are expected to inhibit all aspects of morphogen activity. Even if the specification does not provide a definition for "morphogen

activity," Applicants submit that claims are to be given their broadest plain meaning, in this case, morphogen-stimulated biological activity. A skilled artisan, in view of the instant specification, would have no doubt as to what are the metes and bounds of the term "morphogen activity." Only when "... the scope of the invention sought to be patented cannot be determined from the language of the claims with a reasonable degree of certainty, [is] a rejection of the claims under 35 U.S.C. 112, second paragraph [] appropriate. *In re Wiggins*, 488 F.2d 538, 179 USPQ 421 (CCPA 1973)." Applicants submit that such is not the case here. The plain meaning of "morphogen activity" is just that, and the Office Action fails to present, for example, what activity might or might not be considered to be within the scope of the term, which renders the meaning of the term indefinite.

Similarly, the term "morphogen inhibition" can be interpreted based on its plain meaning. Even if the specification does not explicitly set forth the degree of inhibition, Applicants submit that such degrees of inhibition, like the degree of activity, is unnecessary to define inhibition. For example, if morphogen activity is defined as 100% at the absence of LIF, and if morphogen activity is only 50% at the presence of LIF, then it can be said that there is morphogen inhibition by LIF. A skilled artisan would readily understand without doubt such comparison and the plain meaning of inhibition in view of the specification. Thus reconsideration and withdrawal of the rejection are respectfully requested.

Regarding the recitation of several acronyms such as LIF, etc., Applicants have amended the claims to spell out the full terms in their first occurrence, thus obviating the rejection. However, "OPX" is an arbitrary name defined by the Applicants, and does not have a full term as the other common abbreviations of protein names. Also, the Xenopus protein Vg-1 is its original name rather than an acronym.

In summary, all amended claims fulfill the requirement of 35 U.S.C. 112, second paragraph. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

Date: March 7, 2003

Yu Lu, Ph.D.
Reg. No. 50,306

Customer No: 28120
Docketing Specialist
Ropes & Gray
One International Place
Boston, MA 02110
Phone: 617-951-7000
Fax: 617-951-7050